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ZIKA VIRUS IN TRANSFUSION MEDICINE[1]

ZIKA VÍRUS NA MEDICINA TRANSFUSIONAL

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ABSTRACT

The Zika virus (ZIKV), belonging to the Flaviviridae family, was first discovered in Africa in 1947. It is responsible for the nation-wide rise in arbovirus-related infections in Brazil. Its main transmission pathway relies on the bite or stinging of humans by virus-infected mosquitoes that belong to the Aedes genera, Aedes aegypti being the most common vector, given its wide distribution throughout tropical and subtropical regions. Transfusion-related transmission pathways have been thoroughly discussed recently due to the large number of asymptomatic patients and the virus' strong epidemic potential; however, transmission is also possible through sexual and vertical pathways. Overall, clinical outcomes are positive. The most common symptoms experienced by patients are flu-like and similar to dengue (DENV) and chikungunya (CHIKV) virus infections. Primary diagnosis is based on clinical complaints that are typical in infections with this pathogen accompanied by specific molecular tests, more specifically, real-time reverse transcription polymerase chain reaction (RT-PCR). In a few cases, however, there are reports of severe consequences, including Guillain-Barré Syndrome (SGB), neurological damage and fetal malformations like microcephaly. There are no vaccines or ZIKV-specific antiviral therapies. Thus, the ZIKV remains a threat to hemotherapy infection prevention and leading disease control entities.

Keywords: Dengue, Hemotherapy, Zika Virus.

RESUMO

O vírus Zika é um Flavivírus descoberto na África em 1947, sendo responsável por causar uma arbovirose emergente no Brasil. Seu modo de transmissão é principalmente pela picada de mosquitos infectados do gênero Aedes, sendo que o Aedes aegypti é considerado o vetor mais comum, dada a sua ampla distribuição nos trópicos e subtrópicos; no entanto, também é possível ocorrer a infecção através do ato sexual, materno-fetal, bem como transfusional. Este artigo trata de uma revisão de literatura a qual enfoca o histórico do Zika, sua estrutura viral e patogênese, epidemiologia, manifestações clínicas e diagnóstico, transfusões sanguíneas e os arbovírus. De particular importância, a via de transmissão transfusional tem sido discutida atualmente, devido ao grande número de casos assintomáticos e o potencial epidêmico do Zika em causar epidemias de grandes proporções. De maneira geral, a doença tem quadro clínico benigno, porém consequências clínicas graves têm sido relatadas, tais como a síndrome de Guillain-Barré (SGB), alterações neurológicas e malformações fetais, como microcefalia. Ainda não existem vacinas nem medicamentos antivirais específicos para o Zika, sendo o tratamento apenas de suporte; portanto, medidas de proteção tornam-se importantes para o controle vetorial do mosquito Aedes aegypti. Diante disso, o Zika continua a ser um desafio para a segurança transfusional e organizações líderes de prevenção e controle de doenças.

Palavras-chave: *Dengue, Hemoterapia, Zika Vírus.*

1 Tipo de trabalho?

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INTRODUCTION

Since its onset, only sporadic infections were reported in Africa and Asia, until the first Zika virus (ZIKV) epidemic occurred in the Pacific in 2007, on the Yap Islands (Federated States of Micronesia). In the period between 2013-2014, the virus was responsible for an epidemic in French Polynesia and subsequent spread to all of the Pacific Islands. In 2015, ZIKV emerged in the Americas, more intensively in Latin America and the Caribbean, as well as in Africa (MUSSO *et al*., 2017). The Brazilian Ministry of Health (MS) confirmed its autochthonous transmission in the northeast of the country in May 2015 (CUNHA *et al*., 2016).

The main transmission pathway of the virus to humans is through a mosquito sting by an infected *Aedes.* However, transmission can also occur through sexual, maternal-fetal and transfusion transmission pathways (SLAVOV *et al*., 2016, 2017). In addition, since ZIKV was detected in urine, saliva and in breast milk of humans, other potential transmission pathways must not be excluded (MUSSO *et al*., 2017).

Although signs of ZIKV infection are asymptomatic from 40% to 80% of infected individuals, patients may present nonspecific symptoms that resemble dengue virus (DENV) and chikungunya virus (CHIKV) infections. The most common signs and symptoms manifested by the patients are fever, bilateral non-purulent conjunctivitis, headache, myalgia, arthralgia with peri-articular edema of small joints and maculopapular exanthema (SLAVOV *et al*., 2016, 2017). In addition, cases of neurological manifestations and Guillain-Barré Syndrome (GBS) were considered epidemic in French Polynesia and Brazil. In early 2016, the World Health Organization (WHO) declared the recent ZIKV epidemics as an International Public Health Emergency (ESPII), because of its unexpected causal association with severe congenital brain abnormalities designated by medical entities as congenital Zika Syndrome, especially microcephaly during pregnancy (YUAN *et al*., 2017; BALMASEDA *et al*., 2017).

The primary diagnosis of ZIKV infection is based on the typical clinical symptoms of the patient, as well as a history of recent travels to regions that are endemic with ZIKV, or contact with anyone from those regions (CHEN, TANG, 2016). Differential diagnosis involves molecular tests such as the reverse transcription polymerase chain reaction (RT-PCR), a technique that can be applied in blood, serum, urine, seminal fluid or any other body fluid samples. Laboratorial test results are optimal if performed until one week after the onset of symptoms and the detection of the viral genome by RT-PCR is currently the most sensitive and specific method to confirm the diagnosis of infection by ZIKV (PINTO JUNIOR *et al*., 2015).

Treatments for the infection are symptomatic, since there are no vaccines or antiviral drugs that are specific to ZIKV (PINTO JUNIOR *et al*., 2015). Therefore, protective measures become important for controlling the spread of the disease through vectors, especially the *Aedes aegypti* mosquito

(PINTO JUNIOR *et al*., 2015). In addition, the Centers for Disease Control and Prevention (CDC) recommend that pregnant women avoid unnecessary travels to areas of ZIKV transmission, as well as unprotected sexual contact with a partner who is at risk for HIV infection. Individuals who have traveled to endemic areas should postpone blood donation for at least 28 days (CHEN, TANG, 2016).

The objective of this work was to conduct a literature review on Zika virus infection, with emphasis on the transfusional approach of viral transmission.

ARBOVIRUS

Arboviruses (Arthropod-borne viruses) are viruses transmitted to humans and animals by infected hematophagous arthropods, especially mosquitoes and ticks, through bite, and are classified in this manner because of their replicative cycle, often and continuously replicating in insects (SANTOS, ROMANOS, WIGG, 2015). They are also classified as an RNA virus, very adaptable in nature, being the main reason as to why these viruses are the number one cause of zoonosis (PATY, 2013). This class includes more than 545 species, of which more than 150 are related to human incident zoonosis, diseases of great clinical importance due to the severity of the infections, which are of two types: infections involving the central nervous system (CNS) (myelitis, meningitis, encephalitis, behavioral changes, paralysis, paresis, seizures and coordination problems) and jaundice related hemorrhagic infections (hemorrhagic fevers with hepatic involvement) (VASCONCELOS, CALISHER, 2016).

The Flaviviridae family is composed of three genera: *Flavivirus, Pestivirus* and *Hepacivirus* (LOPES, NOZAWA, LINHARES, 2014). Among arboviruses that affect man, 13 are caused by the *Flavivirus* genus (SANTOS, ROMANOS, WIGG, 2015). The arthropod vectors, belonging to the Diptera order, Culicoidae superfamily and Culicidae family are of greater relevance in the tropics. Mosquitoes of the *Culicidae* family are grouped into three subfamilies: Toxorhynchitinae, Culicinae and Anophelinae, the latter two with a large number of insects with clinical importance. The subfamily Culicinae is the largest subfamily, and the most significant genera that occur in Brazil are: *Aedes, Culex, Sabethes* and *Haemagogus* and the subfamily Anophelinae, which includes the genera *Anopheles* that can also be found in Brazil (CONSOLI, DE OLIVEIRA, 1994).

The *Aedes* genus is the one that most often affects urban environments, with *Aedes aegypti* being the main vector in these types of environment, while *Aedes albopictus* is more widespread in rural areas (WILDER-SMITH *et al*., 2017). These two vectors are located in the tropics and subtropical regions and, preferentially, feed on human blood and are usually synanthropic. In addition, they are more active during the day and their reproduction occurs in domestic and communitary environments with egg incubation and hatching that can occur only in containers with water that sits still for long periods of time (WILDER-SMITH *et al*., 2017).

At least five arboviruses transmitted by mosquitoes to humans have epidemic potential in urban areas such as yellow fever virus (YFV), dengue virus (DENV), West Nile virus (WNV), ZIKV and Chikungunya virus (CHIKV) and have emerged in the hemispheres during recent centuries (GOULD *et al*., 2017), due to multiple factors such as urbanization, globalization and viral mutations that confer greater virulence to some viruses such as zika and chikungunya (WILDER-SMITH *et al*., 2017).

The DENV of the *Flaviviridae* family is the arbovirus of major clinical importance. It is typically found in tropical or subtropical climate and, according to recent estimates, it is responsible for approximately 390 million infections annually, of which 96 million are accompanied by clinical manifestations (BLITVICH, 2016). In addition, the ZIKV (*Flaviviridae* family, *Flavivirus* genus) has acquired clinical prominence through its rapid emergence and dissemination around the Brazilian territory, becoming ESPII due to the severity of clinical symptoms (VASCONCELOS, CALISHER, 2016, WILDER-SMITH *et al*., 2017).

ZIKA VIRUS HISTORY

The first ZIKV isolation occurred in April 1947, through the serum of a febrile Rhesus 766 sentinel monkey, during fieldwork by researchers at the Rockefeller Foundation in the zika forest, a forest reserve of approximately 25 acres, located on the shores of Lake Victory in the province of Entebe in Uganda (DICK, KITCHEN, HADDOW, 1952, BURATTINI, 2017).

The characterization of this *Flavivirus* occurred by coincidence, based on research on the epidemiology of yellow fever (DICK, KITCHEN, HADDOW, 1952). The isolated strain was then named ZIKV766 because of the number of the sentinel monkey. A second isolate of ZIKV was made from a pool of *Aedes africanus* mosquitoes in January 1948, in the same forest, showing the participation of *A. africanus* as a potential vector for this virus (DICK, KITCHEN, HADDOW, 1952). Consequently, in the following 20 years, some isolates of ZIKV were obtained from *Aedes* spp. (*Aedes africanus*) and Malaysia (*Aedes aegypti*), leading to these probable epidemic vectors (MARCHETTE, GARCIA, RUDNICK, 1969, LANCIOTTI *et al*., 2008).

In 1969, ZIKV was isolated from *Aedes aegypt*i mosquitoes collected in Malaysia outside the African continent. Almost a decade later, the first human infections were reported in 1977 on the island of Central Java, Indonesia (MARCHETTE, GARCIA, RUDNICK, 1969). Until the first epidemic on the Yap Islands in the Federated States of Micronesia in April 2007, only 14 cases of ZIKV in humans had been reported, however, none outside the African continent and Southwest Asia (DUFFY *et al*., 2009). Although the epidemic was brief (approximately 3 months), there is serological evidence suggesting that around 70% of islanders were infected with the virus. It demonstrated the high infectivity of ZIKV and its spreading potential as an emerging infectious disease (JIMENEZ *et al*., 2017).

VIRAL STRUCTURE AND PATHOGENESIS

ZIKV belongs to the *Flavivirus* genera and features the same genomic organization as all flaviviruses including DENV, WNV, YFV and Japanese encephalitis virus (JEV) (SHI, GAO, 2017). The ZIKV virions are approximately 60 nm in size and spherical in shape (SHARMA, LAL, 2017). ZIKV has a single-strand positive polarity RNA genome of 10,794 nucleotides with two non-coding regions (5 'NCR and 3' NCR) flanking a single coding sequence (BURATTINI, 2017).

Two species of *Aedes*, *A. aegypt*i and, to a lesser extent, *A. albopictus*, have been linked to almost all known ZIKV epidemics, although two other species, *A. hensilli* and *A. polynesiensis*, were considered to be the vectors in the Yap Islands and French Polynesia, respectively (PETERSEN *et al.*, 2016). Approximately 40 to 80% of individuals infected with ZIKV are asymptomatic (SLAVOV *et al.*, 2017). On average, ZIKV viremia persists for 10 days after infection, symptoms develop after about 6 days and may last for 1 to 2 weeks (FARIA *et al.*, 2017). The incubation period from infection to clinical onset of ZIKV is thought to be 3 to 12 days after the bite of an infected female mosquito (JIMENEZ *et al.*, 2017).

EPIDEMIOLOGY

It is still unknown how the urban migration of this virus occurs (SLAVOV *et al.*, 2016). Probably during heavy rains, the wild mosquito population can progressively grow and spread the virus to nearby villages and from there to large urban centers, so the urban cycle can occur with human-to-human transmission (SLAVOV *et al.*, 2016).

There are reports that the 2007 epidemic in the Yap Islands in the Federated States of Micronesia was the first major worldwide epidemic of ZIKV disease in humans, and only 14 cases had been previously reported (DUFFY *et al.*, 2009).

There are several hypotheses being investigated to address the clinical severity of ZIKV disease in African and Asian continents, as well as the epidemics found in the Pacific Islands and the Americas that are now presenting severe cases, including neurological disease and significant fetal impairment (BURATTINI, 2017). The reasons suggested, but not yet confirmed, why manifestations are worse in severity in those regions include the genetic variation of viral strains, population immunity modulating the clinical presentation of the ZIKV infection because of wide exposure through decades, co-infection with other arboviruses and failures in the systems of identification and registration of cases. (BURATTINI, 2017).

CLINICAL SIGNS & DIAGNOSIS

Although the disease caused by ZIKV is usually self-limiting, there are reports of neurological changes and GBS following an infection by the virus. In adults, severe outcomes were first reported in French Polynesia during the 2013 epidemic. Subsequently an increase in GBS cases has also been reported in Brazil, Colombia, El Salvador, Suriname and Venezuela during the respective ZIKV epidemics (MLAKAR *et al*., 2016, SHAZ, BLOCH, 2017).

Other neurological complications potentially associated with ZIKV infection include encephalitis, meningoencephalitis, transverse and acute myelitis, auditory and ophthalmologic manifestations (MUSSO, GUBLER, 2016). Idiopathic thrombocytopenic purpura has also been reported, which is characterized by severe thrombocytopenia during or after the course of the infection (DA SILVA *et al*., 2017).

Laboratory approaches on the detection of ZIKV include molecular, serological and cultural methods. Most diagnostic tests are done by reference laboratories in the country or state (JIMENEZ *et al*., 2017). The initial diagnosis of the patient is made based on data such as clinical history, travel dates, destinations and activities. During the first week after the onset of symptoms, laboratory diagnosis can be performed using molecular methods such as real-time RT-PCR in blood, urine and/or saliva to detect the virus (JIMENEZ *et al*., 2017). Although serological tests are widely used - such as ELISA and immunofluorescence, they have a relatively high false positive rate in detecting specific IgG and IgM antibodies in the serum sample. Antibodies may be detectable in serum samples within 5 to 6 days of symptomatic disease, but existing tests have low specificity. Consequently, positive results should be confirmed with virus-specific neutralization tests (JIMENEZ *et al*., 2017).

The main routine diagnosis of ZIKV infection is the detection of viral nucleic acid through RT-PCR and the detection of IgM antibodies by enzyme-linked immunosorbent assay (IgM-ELISA) (PETERSEN *et al*., 2016). Therefore, testing of serum samples for RT-PCR obtained within the first week of clinical disease and MAC-ELISA testing of samples that are not tested for RT-PCR or that are considered negative for RT-PCR are considered the most accurate and precise methods of differential diagnosis (PETERSEN *et al*., 2016). Serology for ZIKV is generally tested through ELISA with a platelet neutralization test (PRNT) according to standard protocols. PRNT is the gold-standard for differentiation of anti-*flavivirus* antibodies since it is considered the most specific in primary *flavivirus* differentiation (MUSSO, GLUBER, 2016). However, PRNT is intensely laborious and expensive and is not widely performed (PETERSEN *et al*., 2016).

ARBOVIRUSES AND BLOOD TRANSFUSION

In all blood samples collected, high sensitivity laboratory tests are performed. Serological methods include: hepatitis B surface antigen (HBsAg), hepatitis B virus core antibody (anti-HBc), hepatitis C

(anti-HCV) antibody, human immunodeficiency virus antibody (anti-HIV), human T lymphotropic virus antibody I / II (anti-HTLVI / II), Venereal Disease Research Laboratory (VDRL) anti-*Trypanosoma cruzi* (Chagas disease), while the viral nucleic acid test includes Nucleic Acid Test (NAT) for hepatitis B, C and HIV in order to investigate infectious agents that can be transmitted through blood transfusion pathways (UBIALI, 2015). Up to date, there are no licensed molecular or serological tests for ZIKV screening in blood donors, according to guidelines provided by the Brazilian Association of Hematology, Hemotherapy and Cell Therapy (ABHH) (UBIALI, 2015).

Recent studies have shown that ZIKV can be inactivated in all blood components using Amotosalen combined with ultraviolet A (UVA) in platelets and plasma treated with amustaline (S-303) and glutathione for red blood cells. Both systems use the same mechanism, they react with nucleic acids and modify them to avoid their replication, transcription and translation (LAUGHHUNN *et al.*, 2017). Photochemical treatment using Psoralen (Amotosalen, S-59) in combination with UVA resulted in inactivation of a wide range of viruses, bacteria and protozoa. It is efficient for inactivation of pathogens in platelet and plasma concentrates, but it is not used in red blood cell concentrates, due to poor UVA absorption by the hemoglobin complexes in red blood cells (AUBRY *et al.*, 2016).

The ideal technique for proper diagnosis of viremic samples is through molecular testing for viral RNA detection, but the immediate implementation of these tests for blood donor screening at this time seems unfeasible, not only because of the high cost, but also because ZIKV pathophysiology has not yet been fully elucidated (KASHIMA, SLAVOV, COVAS, 2015, ELLINGSON *et al.*, 2017).

ARBOVIRUS TRANSFUSION RISK

Arboviruses infection prevalence is rising worldwide, representing new risks for patients undergoing blood transfusion therapies (PATY, 2013). The discovery of transfusion transmitted (TT) WNV in the US in 2002 marked a new paradigm, derived from viruses that cause asymptomatic short viremia in infected patients with high incidence of transmissibility, in contrast to some other viruses, such as hepatitis and HIV, where risk of transfusion is only present in patients who have a prolonged carrier state in a population with low and / or unstable incidence of infection (PETERSEN, BUSCH, 2010). Recent discoveries of TT infection by DENV and high prevalence of DENV in blood donations in some countries further justify this concern (PETERSEN, BUSCH, 2010).

The potential for CHIKV TT was demonstrated in the Caribbean during the epidemic in Martinique in 2014, where screening with NAT for CHIKV resulted in four positive plasma samples. Of these donors, two remained asymptomatic and the other two reported febrile syndrome 12 to 24 hours after blood donation (GALLIAN *et al.*, 2014). All arboviruses present a potential risk in TT due to their ability to induce an asymptomatic viremic phase (PATY, 2013). Some examples of arboviruses that produce large epidemics of clinically significant human disease and which are proven or with

potential risks of TT can be seen in table 1 (PETERSEN, BUSCH, 2010).

Table 1 - Arbovirus-related diseases epidemiological distribution.

Organism	Vector	Vertebrate host	Geographical distribution	Syndrome	Transfusion transmission reported
Togaviridae					
Chikungunya	M	Humans, primates	Africa, Asia, Western Pacific	A	No
Rio Ross	M	Marsupials	Australia	A	Yes
Flaviviridae					
Dengue 1-4	M	Humans	Worldwide on the tropics	FH	Yes
Yellow fever	M	Humans, primates	Africa, South America	FH	Yes
Japanese encephalitis	M	Birds, swine	Asia	E	No
St. Louis encephalitis	M	Birds	Americas	E	Yes
WNL encephalitis	M	Birds	Asia, Africa, Americas, Europa	E	Yes
Tick-borne encephalitis (TBE)	T	Rodents	Europa, Asia	E	Yes
Zika	M	Humans, primates	Africa, Asia, Americas, Caribbean, Pacific	CZS, GBS E, A	Yes
Bunyaviridae					
Rift Valley fever	M	Domesticated ungulates, rodents	Africa	FH, E	No

Note: M, mosquito; T, tick; E, encephalitis; HF, Hemorrhagic Fever; A, Arthralgia; CZS, Congenital Zika Syndrome; GBS, Guillain-Barré Syndrome.

TRANSFUSION TRANSMITTED (TT) DENGUE AND ZIKA VIRUS

Screening for DENV has not been implemented because of the low rate of transfusion-transmitted dengue (TTD), although other interventions, including postponing short-term trips even to non-endemic tropical areas and pathogen inactivation technologies, have been largely carried out in endemic areas (MATOS *et al.*, 2016). Screening for DENV in blood donation has been done experimentally in endemic areas, presenting frequencies greater than 1:500 donors positive for DENV RNA, but blood donation screening has not been adopted as a standard protocol (MATOS *et al.*, 2016).

Brazil has one of the largest number of cases of DENV infection and, although there is currently no implementation of donor screening for this arbovirus, it is known that effective preventive measures ought to be adopted by medical entities (LEVI *et al.*, 2015). For proper transfusion safety, the methods targeting DENV RNA (NAT) due to the short viremic phase preceding seroconversion should be performed, as detection of NS1 protein in the blood of suspected cases is a common phenomenon in endemic areas (MATOS *et al.*, 2016). However, a marked decrease in the sensitivity of the tests in analyzed populations has been suggested in recent data, making it an unacceptable option for blood screening, a process that demands maximum sensitivity (MATOS *et al.*, 2016). In contrast,

NAT for DENV was previously implemented in Puerto Rico, following the diagnosis of the hemorrhagic form of the disease occurring in a dialysis patient (LEVI *et al.*, 2015).

The exact impact of ZIKV in blood supplies is uncertain. Current evidence suggests that TT by ZIKV is likely, but clinical penetrance has not been established. Although not unique to ZIKV, measures that are available to protect blood supply include donor selection, blood component quarantine, laboratory screening and / or the use of PRT (JIMENEZ *et al.*, 2017. The application of these measures differs depending on whether they are located in an endemic area versus a non-endemic area (JIMENEZ *et al.*, 2017). In table 2, it is possible to compare the cases of DENV and ZIKV.

Table 2 - Cases of DENV and ZIKV.

Organism	Tt sample	Diagnosis	Number of infected receptors	Geographical distribution	Year	Reference
dENV-1	Red blood cells and fresh plasma	RT-PCR	6	Hong Kong	2002	CHUANG *et al.*, 2008
DENV-2	Red blood cells and fresh plasma	RT-PCR	2	Puerto Rico and Singapore	2007	TAMBYAH *et al.*, 2008
DENV-4	Red blood cells, platelets and fresh plasma	TMA	6	Recife and Rio de Janeiro	2012	LEVI *et al.*, 2015; SABINO *et al.*, 2016.
ZIKV	Red blood cells and platelets	RT-PCR and cell culture	4	Brazil	2016	JIMENEZ *et al.*, 2017

Note: DENV 1, 2 and 4, Dengue virus 1, 2 and 4; ZIKV, Zika virus;
RT-PCR, Real Time-Polimerase Chain Reaction; TMA, Transcription Mediated Amplification.

CONCLUSIONS

ZIKV infection is a serious, worldwide health issue. The possibility of viremic but asymptomatic patients being blood donors represents a serious concern for medical entities responsible for dialysis centers, since ZIKV and others arboviruses' transmission is possible under those circumstances. Uncertainty still remains as to the particular/specific types of receptors susceptible to infection in a clinical exposure. However, recent discoveries suggest relative low-risk for health professionals.

Prevalence studies should be performed in both endemic and non-endemic regions in order to define infectivity through blood components and determine their ability to generate disease in the recipient, especially those at high risk, such as pregnant women and their children.

REFERENCES

AUBRY, M. *et al.* Inactivation of Zika virus in plasma with amotosalen and ultraviolet A illumination. **Transfusion**, v. 56, n. 1, p. 33-40, 2016.

BALMASEDA, A. *et al.* Antibody-based assay discriminates Zika virus infection from other flaviviruses. **Proceedings of the National Academy of Sciences**, v. 114, n. 31, p. 8384-8389, 2017.

BLITVICH, B. Arboviruses: Molecular Biology, Evolution and Control. Nikos Vasilakis and Duane J. Gubler. **The American journal of tropical medicine and hygiene**, v. 95, n. 2, p. 488, 2016.

BURATTINI, M. N. Zika vírus e manifestações clínicas correlatas. In: SALOMÃO, R. (org.). **Infectologia: bases clínicas e tratamento.** Rio de Janeiro: Guanabara Koogan, p. 471-478, 2017.

CHEN, H-L.; TANG, R-B. Why Zika virus infection has become a public health concern?. **Journal of the Chinese Medical Association**, v. 79, n. 4, p. 174-178, 2016.

CHUANG, V. W. M. *et al.* Review of dengue fever cases in Hong Kong during 1998 to 2005. **Hong Kong Medical Journal**, v. 14, n. 3, p. 170, 2008.

CONSOLI, R. A. G. B.; DE OLIVEIRA, R. L. **Principais mosquitos de importância sanitária no Brasil**. SciELO-Editora FIOCRUZ, 1994.

CUNHA, M. S. *et al.* First complete genome sequence of Zika virus (Flaviviridae, Flavivirus) from an autochthonous transmission in Brazil. **Genome Announc.**, v. 4, n. 2, p. e00032-16, 2016.

DA SILVA, I. R. F. *et al.* Neurologic complications associated with the Zika virus in Brazilian adults. **JAMA neurology**, v. 74, n. 10, p. 1190-1198, 2017.

DICK, G. W. A.; KITCHEN, S. F.; HADDOW, A. J. Zika virus (I). Isolations and serological specificity. **Transactions of the royal society of tropical medicine and hygiene**, v. 46, n. 5, p. 509-520, 1952.

DUFFY, M. R. *et al.* Zika virus outbreak on Yap Island, federated states of Micronesia. **New England Journal of Medicine**, v. 360, n. 24, p. 2536-2543, 2009.

ELLINGSON, K. D. *et al.* Cost projections for implementation of safety interventions to prevent transfusion-transmitted Zika virus infection in the United States. **Transfusion**, v. 57, p. 1625-1633, 2017.

FARIA, N. R. *et al.* Establishment and cryptic transmission of Zika virus in Brazil and the Americas. **Nature**, v. 546, n. 7658, p. 406, 2017.

GALLIAN, P. *et al.* Prospective detection of chikungunya virus in blood donors, Caribbean 2014. **Blood**, v. 123, n. 23, p. 3679, 2014.

JIMENEZ, A. *et al.* How do we manage blood donors and recipients after a positive Zika screening result? **Transfusion**, v. 57, n. 9, p. 2077-2083, 2017.

KASHIMA, S.; SLAVOV, S. N.; COVAS, D. T. Zika virus and its implication in transfusion safety. **Revista brasileira de hematologia e hemoterapia**, v. 38, n. 1, p. 90-91, 2016.

LANCIOTTI, R. S. *et al.* Genetic and serologic properties of Zika virus associated with an epidemic, Yap State, Micronesia, 2007. **Emerging infectious diseases**, v. 14, n. 8, p. 1232, 2008.

LAUGHHUNN, A. *et al.* Amustaline (S-303) treatment inactivates high levels of Zika virus in red blood cell components. **Transfusion**, v. 57, n. 3pt2, p. 779-789, 2017..

LEVI, J. E. *et al.* Real-time symptomatic case of transfusion-transmitted dengue. **Transfusion**, v. 55, n. 5, p. 961-964, 2015.

LOPES, N.; NOZAWA, C.; LINHARES, R. E. C. Características gerais e epidemiologia dos arbovírus emergentes no Brasil. **Revista Pan-Amazônica de Saúde**, v. 5, n. 3, p. 55-64, 2014.

MARCHETTE, N. J.; GARCIA, R.; RUDNICK, A. Isolation of Zika virus from Aedes aegypti mosquitoes in Malaysia. **The American journal of tropical medicine and hygiene**, v. 18, n. 3, p. 411-415, 1969.

MATOS, D. *et al.* Probable and possible transfusion-transmitted dengue associated with NS1 antigen--negative but RNA confirmed-positive red blood cells. **Transfusion**, v. 56, n. 1, p. 215-222, 2016.

MLAKAR, J. *et al.* Zika virus associated with microcephaly. **New England Journal of Medicine**, v. 374, n. 10, p. 951-958, 2016.

MUSSO, D.; GUBLER, D. J. Zika virus. **Clinical microbiology reviews**, v. 29, n. 3, p. 487-524, 2016.

MUSSO, D. *et al.* Molecular detection of Zika virus in blood and RNA load determination during the French Polynesian outbreak. **Journal of medical virology**, v. 89, n. 9, p. 1505-1510, 2017.

PATY, M. C. Expansion des arboviroses et gestion du risque transfusionnel: exemple des virus West Nile, de la dengue et du chikungunya. **Transfusion clinique et biologique**, v. 20, n. 2, p. 165-173, 2013.

PETERSEN, E. *et al.* Rapid spread of Zika virus in the Americas-implications for public health preparedness for mass gatherings at the 2016 Brazil Olympic Games. **International Journal of Infectious Diseases**, v. 44, p. 11-15, 2016.

PETERSEN, L. R.; BUSCH, M. P. Transfusion-transmitted arboviruses. **Vox sanguinis**, v. 98, n. 4, p. 495-503, 2010.

PINTO JUNIOR, V. L. P. *et al.* Zika virus: a review to clinicians. **Acta medica portuguesa**, v. 28, n. 6, p. 760-765, 2015.

SABINO, E. C. *et al.* Transfusion-transmitted dengue and associated clinical symptoms during the 2012 epidemic in Brazil. **The Journal of infectious diseases**, v. 213, n. 5, p. 694-702, 2015.

SANTOS, N. S. O.; ROMANOS, M. T. V.; WIGG, M. D. **Virologia humana.** Grupo Gen-Guanabara Koogan, 2015.

SHARMA, A.; LAL, S. K. Zika virus: transmission, detection, control, and prevention. **Frontiers in microbiology**, v. 8, p. 110, 2017.

SHI, Y.; GAO, G. F. Structural biology of the Zika virus. **Trends in biochemical sciences**, v. 42, n. 6, p. 443-456, 2017.

SLAVOV, S. N. *et al.* Zika virus RNA detection in asymptomatic blood donors during an outbreak in the northeast region of São Paulo State, Brazil, 2016. **Transfusion**, v. 57, n. 12, p. 2897-2901, 2017.

SLAVOV, S. N. *et al.* Overview of Zika virus (ZIKV) infection in regards to the Brazilian epidemic. **Brazilian journal of medical and biological research**, v. 49, n. 5, 2016.

TAMBYAH, P. A. *et al.* Dengue hemorrhagic fever transmitted by blood transfusion. **New England Journal of Medicine**, v. 359, n. 14, p. 1526-1527, 2008.

UBIALI, E. M. A. O processo hemoterápico e as etapas do ciclo do sangue. **Voluntária de Sangue**, p. 21, 2015.

VASCONCELOS, P. F. C.; CALISHER, C. H. Emergence of human arboviral diseases in the Americas, 2000-2016. **Vector-borne and zoonotic diseases**, v. 16, n. 5, p. 295-301, 2016..

WILDER-SMITH, A. *et al.* Epidemic arboviral diseases: priorities for research and public health. **The Lancet infectious diseases**, v. 17, n. 3, p. e101-e106, 2017.

YUAN, L. *et al.* A single mutation in the prM protein of Zika virus contributes to fetal microcephaly. **Science**, v. 358, n. 6365, p. 933-936, 2017.